REMARKS/ARGUMENTS

Status of the Claims

Upon entry of the present amendment, claims 26-37 and 52-58 are pending. Claims 26-34 are withdrawn from consideration. Claims 26 and 35-37 are amended. New claims 52-58 are added.

Claim 26 is amended to set forth detecting "a deficiency in immune cell function." Support is found, for example, in the legends for Figures 3-5, on page 6, lines 12-20 and in Figures 3-5. Claim 26 is further amended to recite "at least one of" instead of "either or both." Claim 26 is also amended set forth that the second type of diagnostic reagent binds to a glycoconjugate that has an oligosaccharide determinant that is absent or present at reduced levels on glycoconjugates in a sample obtained from a mammal that has the deficiency in immune cell function. Support is found, for example, in Figures 3-5.

Claim 35 is amended for proper antecedent basis and to set forth that the deficiency is in myeloid cell function. Support is found, for example, on page 28, lines 10-12 and on page 37, lines 8-10.

Claim 36 is amended for proper antecedent basis.

Claim 37 is amended to set forth that the diagnostic reagent comprises an antibody that specifically binds to an immune cell surface protein selected from the group consisting of a CD45 isoform and a CD43 glycoform. Support is found, for example, on page 6, lines 18-20; on page 7, lines 26-29; and on page 41, line 25 through page 42, line 2.

New claim 52 finds support, for example, on page 37, lines 3-10.

New claims 53-56 find support, for example, in Figures 3-5.

New claim 57 sets forth a method of diagnosing a deficiency in an inflammatory response resulting from a deficiency in core 2 GlcNAc transferase activity. Support is found, for example, on page 6, lines 18-20 and in Figure 5.

New claim 58 finds support, for example, on page 6, lines 18-20; on page 7, lines 26-29; and on page 41, line 25 through page 42, line 2.

Objections to the Specification

In accordance with the suggestion of the Examiner, Applicants have inserted a new paragraph that sets forth priority applications.

Rejection under 35 U.S.C. § 112, second paragraph

The Examiner rejected claim 26 for reciting "either or both." In response, applicants have amended claim 26 to recite "at least one."

The Examiner rejected claim 37 for "recitation of antibodies B220 and 1B11." In response, Applicants have amended claim 37 to clarify that the methods can be carried out using any antibody that specifically binds to Core 2 type O-glycans on an immune cell surface protein selected from the group consisting of a CD45 isoform and a CD43 glycoform.

Claim 36 is rejected for the recitation of "reduced binding." In response, Applicants have amended base claim 26 to set forth that a second type of diagnostic agent binds to a glycoconjugate that has an oligosaccharide determinant that is present at reduced levels on glycoconjugates in a sample obtained from a mammal that has a deficiency in immune cell function.

Rejection under 35 U.S.C. § 112, first paragraph, enablement requirement

The Examiner has rejected claims 26 and 35-37 under 35 U.S.C. § 112, first paragraph, as allegedly failing to comply with the enablement requirement. This rejection is respectfully traversed because Applicants have shown those of skill in the art how to carry out the present methods commensurate with the scope of the amended claims.

As amended, claim 26 is directed to a method of detecting a deficiency in immune cell function by contacting a sample from a mammal with a diagnostic reagent that binds to a glycoconjugate that has an oligosaccharide determinant. The deficiency in immune cell function is detected by determining a differential presence of the oligosaccharide determinant in samples

from individuals that have and individuals that do not have the deficiency in immune cell function.

As the Examiner knows, the test of enablement is whether one reasonably skilled in the art could make or use the invention from the disclosures in the patent coupled with information known in the art without undue experimentation. M.P.E.P. § 2164.01, *citing United States v. Telectronics, Inc.* 857 F.2d 778, 785; 8 USPQ2d 1217, 1223 (Fed. Cir. 1988). A patent need not teach, and preferably omits, what is well known in the art. *Id.*, *citing Hybritech, Inc. v. Monoclonal Antibodies, Inc.* 802 F.2d 1367, 1384; 231 USPQ 81, 94 (Fed. Cir. 1986).

Here, Applicants methods utilize detection techniques well known to those in the art at the time of the December 2, 1998 priority date for the present invention (*i.e.*, flow cytometry). Using conventional detection methods, Applicants have shown those of skill in the art how to detect a deficiency in immune cell function due to the deficient functioning of a glycosyltransferase enzyme in at least three different working examples.

In a first example, Applicants show that a deficiency of ST6Gal sialyltransferase activity can result in a deficiency in B cell immune response function that can be detected by evaluating the differential binding of an anti-CD22 antibody and *Sambucus nigra* lectin (SNA) (page 6, lines 12-14 and Figure 3 of WO 00/33076) to lymphoid cells. Figure 3 shows that mixed populations of cells were evaluated, and lymphoid, myeloid and erythroid cell populations were separated or "gated" using cell separation or flow cytometry techniques well known in the art.

In a second example, Applicants show that a deficiency of ST3Gal I sialyltransferase activity can result in a deficiency in T cell function that can be detected by evaluating the differential binding of the lectins peanut agglutinin (PNA), *Maackia Amurensis* II (MAL II), and Jacalin (JAC) to splenocytes, which are comprised of mixed immune cell populations (*Id.* at page 6, lines 15-17 and Figure 4).

In a third example, Applicants show that a deficiency of Core 2 GlcNAc transferase activity can result in a deficient inflammatory response that can be detected by evaluating the differential binding of antibodies against CD45 and CD43 to cell surface glycoproteins on splenocytes (*Id.* at page 6, lines 18-20 and Figure 5).

This third example demonstrates that one can detect for an immune function deficiency resulting from a deficiency in glycosyltransferase activity on an immune cell type other than the immune cell manifesting the deficient function. There is a dichotomy between detection of the immune function deficiency and the actual immune cell with deficient function. Example 2 (*Id.* at page 36, line 26 through page 48, line 14) discusses that a deficiency of Core 2 GlcNAc transferase does not affect lymphocyte homing, but Figure 5 shows that the B-cell specific form of CD45 (B220) is differentially detected on splenocytes from mice having or lacking a Core 2 GlcNAc transferase gene. Figure 5 shows that one can detect for a deficiency in neutrophil function by differentially detecting for an oligosaccharide determinant on B-cells or undifferentiated CD43+ myeloid cells.

Applicants teachings are applicable to other immune cell function deficiencies resultant from deficient glycosyltransferase activity. Applicants show that the methods can be practiced by detecting for the differential presence of an oligosaccharide determinant on a mixed population of immune cells. It is not necessary to separately identify the immune cell types, although this can be done using antibodies specific for particular cell populations (*e.g.*, B-cells or T-cells) or by flow cytometry gating (forward and side scatter to isolate detection myeloid cells; *see*, *Id.* at page 7, line 30). Applicants further teach which lectins can be used to detect for particular glycosyltransferase deficiencies in Table 1 on page 18, line 3 through page 19, line 4.

The Examiner is concerned that the present detection methods are not applicable to known human diseases. Firstly, Applicants demonstrate that a Core 2 GlcNAc transferase deficiency results in neutrophilia in mice (*see*, page 37, lines 3-4 and page 42, lines 7-19), a human disease condition recognized by those of skill in the art.[1] Applicants have further demonstrated that a ST6Gal sialyltransferase deficiency results in defective B-cell activation and that a ST3Gal I sialyltransferase deficiency results in defective T-cell function, also recognized disease conditions. Applicants attach to this amendment as Exhibit B pages 10:11-10:21 from Janeway, *et al.*, *ImmunoBiology*, 3rd Edition, 1997, which discusses inherited (*i.e.*, genetically transmitted) immunodeficiency diseases. Janeway, *et al.* demonstrates that inherited immune

[1] *See, for example*, pages 351-353 from *Harrison's Principles of Internal Medicine*, Kaspar, *et al.*, eds., 16th ed., 2005, attached as Exhibit A.

cell function deficiencies can result in increased susceptibility to infections. The type of infection to which a host will have increased susceptibility depends on the type of immune cell with deficient function regardless of the reason for the deficient immune cell function. For example, Section 10-10 on pages 10:17-10:18 discusses that phagocytic cell defects permit widespread bacterial infections. Therefore, that an individual with an inherited defect in a glycosyltransferase enzyme (*i.e.*, a Core 2 GlcNAc transferase) that results in defective phagocytic cell (*i.e.*, neutrophil) function will have increased susceptibility to bacterial infections. Similarly, an individual with an inherited defect in a glycosyltransferase enzyme (*i.e.*, a ST6Gal sialyltransferase) that results in defective B-cell activation (*see*, page 55, lines 5-13 and page 56, line 24 through page 57, line 8 of WO 00/33076) will have increased susceptibility to extracellular bacterial infections (*see*, page 10:12-10:15 of Janeway, *et al.*). Likewise, an individual with an inherited defect in a glycosyltransferase enzyme (*i.e.*, a ST3Gal I sialyltransferase) that results in defective T-cell function (*see*, page 60, lines 17-24 of WO 00/33076) will have increased susceptibility to viral and/or bacterial infections (*see*, pages 10:12, 10:15-10:16 and 10:18-10:21 of Janeway, *et al.*).

In summary, Applicants provide detailed guidance and at least three different working examples on how to carry out the claimed methods. Applicants further teach how the methods are applicable to detecting any immune cell function deficiency due to a deficiency of glycosyltransferase activity by detecting the presence, absence or presence at reduced levels of an oligosaccharide determinant using techniques well known in the art. The examples in the specification and Janeway, *et al.*, which reflects the knowledge of those of skill in the art, demonstrate how the present methods are applicable to human disease conditions. Accordingly, the Examiner is respectfully requested to withdraw this rejection because Applicants have taught those of skill in the art how to practice the claimed methods without undue experimentation.

Rejection under 35 U.S.C. § 112, first paragraph, written description requirement

The Examiner has rejected claims 26 and 35-37 under 35 U.S.C. § 112, first paragraph, for allegedly failing to comply with the written description requirement.

Compliance with the written description requirement is found when the claimed subject matter is described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. Possession can be shown in a variety of ways, including description of reduction to practice. M.P.E.P. § 2163(I).

As an initial matter, Applicants respectfully submit that the present rejection is improper for failure to meet the proper standards for a written description rejection. The essential goal of the description of the invention requirement is to clearly convey the information that an applicant has invented the subject matter which is claimed. *Id.* Here, the claims are directed to methods of detection of deficiency of immune cell function resulting from deficient glycosyltransferase activity. As described above, Applicants have provided three separate working examples describing how to successfully practice the present methods. Applicants have further described how the methods relate to diagnosing human disease conditions resulting from deficient immune cell function. The Examiner's objection to the recitation of the phrase "myeloid deficiency" in the claims has been rendered moot by elimination of this language.

This rejection is respectfully traversed because Applicants have described the present methods commensurate with the scope of the amended claims. The present invention is based, in part, on the discovery that deficiencies in glycosyltransferase activity can result in deficiencies in immune cell function. Deficient glycosyltransferase activity can be detected on the surface of immune cells by the presence, absence or reduced presence of glycoconjugates having particular oligosaccharide determinants. Applicants specifically demonstrate how the claimed methods can be practiced in a mammal that has deficient ST6 Gal, ST3 Gal I, or Core 2 GlcNAc glycosyltransferase activity by detecting for the presence, absence or reduced presence of oligosaccharide determinants on the surface of mixed populations of immune cells (*i.e.*, peripheral blood or splenocytes) using antibodies and/or lectins (*see*, for example, page 6, lines 12-20 and Figures 3-5; page 28, lines 6-18 and page 29, line 11 through page 30, line 31). Applicants further describe how the present methods generally can be practiced to detect reduced glycosylation activity due a defect in any glycosyltransferase employing antibodies or lectin binding components that specifically bind to oligosaccharide determinants (*see*, page 16, line 5

through page 20, line 8). Applicants further describe labeling the binding components (page 20, line 9 through page 21, line 30), sources for test samples (page 22, lines 1-27), and assay formats based on assays known to those of skill in the art (page 22, line 28 through page 23, line 31). Importantly, Applicants teachings show that regardless of the particular defective glycosyltransferase or the particular immune cell type with resultant deficient function, the steps of the present detection methods remain the same (*see*, page 35, line 14 through page 36, line 2).

Because Applicants have described the presently claimed methods in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors had possession of the claimed invention, the Examiner is respectfully requested to withdraw this rejection.

CONCLUSION

In view of the foregoing, Applicants believe all claims now pending in this Application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 925-472-5000.

Respectfully submitted,

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